Diagnosis of acute myocardial infarction in the presence of left bundle-branch block

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Key questions

What is already known about this subject?

Patients with suspected acute myocardial infarction (AMI) in the setting of left bundle branch block (LBBB) present an important diagnostic and therapeutic challenge to the clinician.

What does this study add?

Specific ECG criteria in LBBB patients including concordant ST-segment elevation (criteria 1) or depression (criteria 2) or pronounced discordant ST-segment elevation (criteria 3) in specific ECG leads and an alternative ECG criteria including ST-segment depression or elevation discordant with the QRS complex with a magnitude of at least 25% of the QRS complex (alternative criteria 3) together with suggested (h)s-cTn thresholds (e.g. hs-cTnT ≥42ng/l at presentation) allow an accurate and immediate triage to coronary angiography in patients with LBBB and symptoms suggestive of AMI.

How might this impact on clinical practice?

An integrated triage-algorithm including specific ECG criteria with high specificity, as well as hs-cTnT/I concentrations at presentation and their 0/1h- or 0/2h-changes provides high diagnostic accuracy and efficacy helping in the selection of patients for immediate and/or early coronary angiography.

ABSTRACT

Objective: Patients with suspected acute myocardial infarction (AMI) in the setting of left bundle branch block (LBBB) present an important diagnostic and therapeutic challenge to the clinician.

Methods: We prospectively evaluated incidence of AMI, and diagnostic performance of specific electrocardiographic (ECG) and high-sensitivity cardiac troponin (hs-cTn) criteria in patients presenting with chest discomfort to 26 emergency departments in three international, prospective, diagnostic studies. The final diagnosis of AMI was centrally adjudicated by two independent cardiologists according to the universal definition of myocardial infarction.

Results: Among 8830 patients, LBBB was present in 247 patients (2.8%). AMI was the final diagnosis in 30% of patients with LBBB, with similar incidence in those with known LBBB versus those with presumably new LBBB (29% vs 35%, p=0.42). ECG criteria had low sensitivity (1-12%), but high specificity (95-100%) for AMI. The diagnostic accuracy as quantified by the receiver-operating-characteristics curve of hs-cTnT and hs-cTnI concentrations at presentation (AUC 0.91; 95%CI 0.85–0.96 and 0.89; 95% CI 0.83-0.95) as well as that of their 0/1h- and 0/2h-changes was very high. A diagnostic algorithm combining ECG criteria with hs-cTnT/I concentrations and their absolute changes at 1h or 2h derived in cohort 1 (45 of 45 (100%) of patients with AMI correctly identified), showed high efficacy and accuracy when externally validated in cohort 2&3 (28 of 29 patients, 97%).

Conclusion: Most patients presenting with suspected AMI and LBBB will be found to have diagnoses other than AMI. Combining ECG criteria with hs-cTnT/I testing at 0/1h or 0/2h allows early and accurate diagnosis of AMI in LBBB.

Keywords

73 left bundle branch block, electrocardiography, high sensitivity cardiac troponin; acute

74 myocardial infarction

75 **Registration Numbers**

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INTRODUCTION

Patients with symptoms suggestive of acute myocardial infarction (AMI) account for approximately 10% of all emergency department (ED) consultations. Rapid identification of AMI as life-threatening disorder is important for the early initiation of highly effective, evidence-based therapy.(1)(2)(3) Patients presenting with suspected AMI and left bundle branch block (LBBB) to the ED represent a unique diagnostic and therapeutic challenge, as altered ventricular depolarization masks changes in ventricular repolarization associated with myocardial ischemia.(2)

In patients presenting with ST-segment elevation MI (STEMI), who usually can be rapidly identified with the 12-lead ECG, enormous improvements in outcomes have been achieved.(1)(2) These patients derive major benefit from immediate coronary reperfusion.(1)(2) It is currently unknown, how AMI can best be diagnosed early in patients presenting with suspected AMI and LBBB.(1)(2) This major uncertainty is highlighted by divergent recommendations given by the respective clinical practice guidelines in the United States and Europe.(1)(2) Current European Society of Cardiology (ESC) guidelines stated that patients with LBBB should be managed in a way similar to STEMI patients.(2) In contrast, current American Heart Association (AHA) and American College of Cardiology (ACC) guidelines interpret LBBB not to be diagnostic for AMI.(1) Too liberal interpretation of LBBB could lead to thousands of unnecessary cardiac catheterization laboratory activations and thousands of patients inappropriately given thrombolytic therapy each year, increased risk of complications related to inappropriate invasive procedures, prolonged hospitalization, higher treatment costs and decreased quality of life for patients.(4)(5)(6) In contrast, too restrictive interpretation of LBBB could withhold life-saving immediate reperfusion therapy from patients with large AMIs and could ultimately increase mortality.(4)(7)

In order to address this important gap in knowledge, we aimed to first, evaluate the incidence of AMI among patients with suspected AMI and LBBB in the recorded at ED presentation, and second, to develop a comprehensive strategy for the early diagnosis of AMI in patients with LBBB.(4)(8)(9)

METHODS

Study design and oversight

We enrolled adult patients presenting with suspected AMI to the ED in three large prospective multicenter diagnostic studies carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committees. These are Advantageous Predictors of Acute Coronary Syndrome Evaluation (APACE) (10)(11)(12) Accelerated Diagnostic Protocol to Assess patients with chest Pain symptoms using contemporary Troponins as the only biomarker (ADAPT),(13) and High-sensitivity cardiac Troponin T assay for RAPID rule-out of AMI (TRAPID-AMI)(14). Written informed consent was obtained from all patients (**Online Table 1**).

The authors designed the study, gathered, analyzed and reported the data according to the STARD guidelines for studies of diagnostic accuracy(15) (**Online Table 2),** vouch for the data and analysis, wrote the paper, and made the decision to submit it for publication. The sponsors had no role in the design of the study, the analysis of the data, the preparation of the manuscript, or the decision to submit the manuscript for publication.

Methodology of all three cohorts

In all three cohorts, we included unselected patients presenting to the ED with acute chest discomfort. All patients underwent a clinical assessment that included standardized and detailed medical history including assessment of chest pain characteristics, vital signs, physical examination, 12-lead ECG, continuous ECG rhythm monitoring, pulse oximetry, standard blood test, and chest radiography and echocardiography if indicated. Treatment of patients was left to discretion of the attending physician.

Detailed methodical descriptions of all 3 cohorts including study -design, -dates and -centers, eligibility criteria and study population, routine clinical assessment, adjudication of final diagnoses, follow-up and clinical endpoints are shown in the Appendix. An overview of study specific characteristics including investigational high-sensitivity cardiac troponin (hs-cTn) measurements, adjudication of final diagnoses and specific ECG criteria for all 3 cohorts are shown in **Online Table 1** and described in detail within the Appendix.

Adjudication of specific ECG criteria

ECG adjudication was performed centrally for all 3 cohorts by at least 2 independent cardiologists blinded to all clinical information and using predefined criteria.(16)(17) LBBB criteria were a QRS duration of more than 120ms, dominant S wave in V1, broad monophasic R wave in lateral leads (I, aVL, V5-V6), an absence of Q waves in lateral leads (I, V5-V6; small Q waves were still allowed in aVL) and prolonged R wave peak time > 60ms in left precordial leads (V5-6).

ECG criteria 1 to 3(16) included ST-segment elevation of 0.1 mV or more concordant with the QRS complex in any lead (ECG criteria 1, 5 points), concordant ST-segment depression of 0.1 mV or more in lead V1, V2, or V3 (ECG criteria 2, 3 points) and ST-segment elevation of 0.5 mV or more discordant with the QRS complex in any lead (ECG criteria 3, 2 points; **Online Figure 1A**). A score of ≥3 was suggested for the diagnosis of acute coronary occlusion within the original publication (ECG score ≥3).(16) The alternative ECG criteria 3 (17) were proposed to be superior to the original ECG criteria 3 and is defined as a negative ST/S ratio <-0.25 and at least 0.1 mV of ST segment elevation in any lead, (alternative ECG criteria 3, 2 points, **Online Figure 1B**)(18). Again, a score of ≥3 was suggested for the diagnosis of acute coronary occlusion (alternative ECG score ≥3). In case of

153 presence of LBBB on a previous ECG, LBBB was classified as known. Otherwise it was
154 classified as presumably new. A differentiation between new and new presumably LBBB was
155 not possible, because exact onset of LBBB could not be determined in most patients.
156 Differentiation between known and presumably new LBBB was possible in cohort #1 by
157 retrieving previous ECG recordings from the electronic ECG storage systems of the
158 participating institutions as well as the general practitioner in the vast majority of patients, but
159 not in cohort #2 and #3.

160 Case studies for three patients presenting with suspected AMI and LBBB are
161 described in **Online Figure 2,** including their clinical presentation, medical history, ECG at
162 presentation, hs-cTnT concentrations, coronary angiography results, follow-up information
163 and adjudication diagnoses.

164

165 **Statistical analysis**

166 The data are expressed as medians ± interquartile range (IQR) for continuous
167 variables, and for categorical variables as numbers and percentages. All variables between
168 known LBBB and presumably new LBBB or LBBB with or without AMI were compared by
169 Student`s t Test or Mann-Whitney-U test for continuous variables or Pearson chi-square or
170 Fisher's Exact test for categorical variables. Receiver-operating characteristics (ROC) curves
171 were constructed to assess the sensitivity and specificity for concentrations of hs-cTnT/I at
172 presentation and their 1h or 2h absolute changes. A positive predictive value (PPV) of 80%
173 was considered necessary to proceed with early coronary angiography(19) for the derivation
174 of cut-off concentrations. In cohort #1 (derivation cohort) we performed a univariate
175 regression analysis using the selection operator LASSO to find predictors for the model.
176 Variables who entered this model have been previously selected based on their availability in

all 3 cohorts, shown differences within the baseline characteristics tables and based on their clinical importance. Additionally, the numbers of variables were restricted to the number of events (AMI in patients with LBBB). In cohort #2 and cohort #3 (validation cohorts) we used the same variables as in cohort #1, if they have shown a statistically significant difference. All hypothesis testing was two-tailed, and P values of less than 0.05 were considered to indicate statistical significance. All statistical analyses were performed with the use of IBM SPSS Statistics for Windows, version 24.0 (SPSS Version 24, Inc Chicago, IL).

Results

Study population

Overall, 8830 patients were available for analysis (**Online Figure 3**). LBBB was present in 247 patients (2.8%; **Figure 1A**)). AMI was the final diagnosis in 30% (75 of 247 patients, **Figure 1B**) of patients with LBBB, with similar incidence in those with known LBBB versus those with presumably new LBBB (29% vs 35%, p=0.42). Patients with known LBBB had similar baseline characteristics as those with presumably new LBBB. (**Online Table 3**) Patients with LBBB were older, had more cardiovascular risk factors and more often preexisting cardiac disease, including coronary artery disease (CAD) in 54% as compared to 33% in the overall population (**Table 1, Online Tables 4-8**).

Echocardiography

Echocardiographic findings were similar in LBBB patients with AMI as compared to LBBB patients without AMI (**Online Table 9**). Most patients with LBBB had moderately reduced left ventricular ejection fraction (LVEF, median 40%), a dilated left atrium (70%), left ventricular hypertrophy (56%) and wall motion abnormalities (79%).

Coronary intervention

In patients with AMI and LBBB coronary intervention were performed in the left anterior descending coronary artery in 16%, in the left circumflex artery in 13%, in a venous bypass graft in 8.9%, and in the right coronary artery in 4.4% (**Table 1**).

ECG criteria

Seventeen patients (12%) fulfilled at least one of the specific ECG criteria for AMI detection. Each criteria or their combination in a score had a sensitivity ranging from 1% to 12% and a specificity ranging from 95% to 100% (**Table 2, Online Figure 4A**). We found no differences for specific ECG criteria pertaining to the culprit lesion. Thirteen percent of patients with specific ECG criteria were found to have the culprit lesion in the left main vessel, RIVA, RCX or ACD, respectively.

Hs-cTnT/I

Blood concentrations of hs-cTnT and (h)s-cTnI at presentation and their early absolute changes were significantly higher in LBBB patients with AMI as compared to those with other final diagnoses **(Online Figure 5**). Diagnostic accuracy as quantified by the area under the ROC curve (AUC) was very high (at presentation AUC for hs-cTnT 0.91; 95%CI 0.85–0.96; and AUC for hs-cTnI 0.89, 95% CI 0.83-0.95; **Table 3**). Hs-cTnT levels ≥42ng/L (hs-cTnI ≥45ng/L, s-cTnI ≥52ng/L) provided a PPV of 80% (95% CI, 64-90%) for AMI and together with known CAD (odds ratio 4.6, 95%CI 2.0–10.4) predicted AMI in multivariate analysis in LBBB patients (odds ratio 31.4, 95%CI 10–98.7; **Table 3; Online Table 10, Online Figure 4B**).

Suggested diagnostic work-up

In cohort #1 at least one specific ECG criteria were positive in 17/140 (12%) of patients with LBBB and suspected AMI, of whom 8 (47%) patients had an AMI. 38/140 patients had hs-cTnT concentration at presentation ≥ 42ng/L, of whom 29 (76%) patients had an AMI. 11/140 (8%) had an hs-cTnT 0/1h absolute change concentration ≥ 3ng/L, of whom 8 (73%) had an AMI (**Figure 1**). In both validation cohorts using this step-by-step approach resulted in similar findings and high accuracy to identify patients for the suggested work-up. (**Figure 2 and 3**).

The performance of the individual ECG criteria, of hs-cTnT and hs-cTnI in general, and their respective cut-off concentrations optimized for use in patients with LBBB in particular, were similar among the three cohorts.

DISCUSSION

This analysis is based on three large prospective multicenter diagnostic studies with central adjudication of AMI by independent cardiologists applying the universal definition of AMI(3). It was performed to contribute to advancing the clinical care of patients presenting with symptoms suggestive of AMI and LBBB to the ED. We report five major findings.

First, 2.8% of patients presenting with suspected AMI to the ED had LBBB. These patients were older and more often had preexisting cardiovascular disorders including CAD. Second, the majority of patients presenting with suspected AMI and LBBB were finally found to have non-cardiac disorders and cardiac disorders other than AMI. The incidence of AMI was 30% in LBBB patients, and similar in patients with known LBBB versus new/presumably new LBBB. Third, specific ECG criteria had low sensitivity, but high specificity for AMI. Integrating the alternative ECG criteria 3 to the specific ECG score resulted in a sensitivity of 12% and specificity of 97%. Fourth, diagnostic accuracy of hs-cTnT and hs-cTnI concentrations at ED presentation and their early changes within 1h or 2h was very high. In addition, together with a history of known CAD hs-cTnT/I concentrations at presentation predicted the presence of AMI in multivariate analysis. Hs-cTnT concentrations at presentation with a predefined PPV of at least 80% for AMI were 42ng/L or higher (hs-cTnI ≥45ng/L, s-cTnI ≥52ng/L). Interestingly, these (h)s-cTnT/I cut-off levels providing a PPV for AMI of 80% in patients with LBBB were similar to those recommended in current ESC guidelines for the rule-in of AMI in general. (20) Fifth, a novel triage algorithm integrating specific ECG criteria as the first step, hs-cTnT/I at presentation as the second, and the 0/1h absolute change in hs-cTnT/I as the third step, provided high accuracy and efficacy for the early detection of AMI and thereby for the selection of patients for immediate and early coronary angiography in both the derivation and external validation cohort.

These findings from 8830 patients presenting with suspected AMI to the ED extend and corroborate previous work on patients with LBBB.(16)(17)(21)(22)(23)(24)(25)(26) Results derived from selected patients enrolled in clinical trials of new pharmacologic therapies had indicated that patients with likely AMI who have new or presumably new LBBB should undergo rapid reperfusion therapy.(2) This strategy has recently been challenged by retrospective single-center studies from unselected ED cohorts or STEMI-networks suggesting that most patients with symptoms suggestive of AMI with new or presumably new LBBB do not have AMI.(23)(24)(27)(28)(29)(30) However, these studies had important methodological limitations including retrospective design, use of administrative coding for AMI, use of cardiac biomarkers with poor sensitivity such as CK-MB or previous generation cTn, and lack of adherence to the universal definition of AMI.(1)(2)

Our study overcomes these limitations and provides detailed guidance on how currently available diagnostic tools can best be used in patients with LBBB to balance the benefits and risks associated with early coronary angiography.(1)(2) Only one third of patients presenting with symptoms suggestive of AMI and LBBB to the ED will be found to have AMI as final diagnosis, irrespective of known or presumably new LBBB. Due to their high specificity, specific ECG criteria should be used to immediately triage patients towards rule-in of AMI and immediate coronary angiography such as in STEMI patients (around 6-12% of patients with LBBB). Patients not meeting these ECG criteria do have only a slightly higher overall incidence of AMI as compared to patients without LBBB and should undergo standard testing for hs-cTn.(1)(2)(8)(13)(14) Already the measurement at presentation provides very high diagnostic accuracy and allows to rapidly rule-in additional patients for early coronary angiography, if hs-cTn blood concentrations are substantially elevated (≈15% of patients with LBBB).(8)(13)(14)(20) In all remaining patients, the second hs-cTn blood concentration determined 1h to 2h after presentation will allow to identify additional AMI

patients in case of a relevant absolute change and triage them for early coronary angiography. In patients not meeting any of the three rule-in criteria, the likelihood of having AMI is very low. Still, as with all other early triage algorithm, detailed clinical assessment including chest pain characteristics and possibly additional hs-cTnT/I measurements at 3h helps selecting the most appropriate cardiac imaging modality to follow: echocardiography, non-invasive stress imaging, coronary computed tomography angiography, coronary angiography, or none in patients in whom the diagnostic work-up already has established a definite alternative cause of acute chest discomfort at that time such as pneumonia or pulmonary embolism (**Figures 1-3 and Online Figure 6A-B**).(19)

Among LBBB patients with AMI, culprit lesions most often were in the RIVA and RCX. This distribution differs from all-comers with AMI. (16)(17)(21)(22)(23)(24)(25)(26)

Potential limitations of the present study merit consideration. First, while a relevant percentage of patients had LBBB recorded on a previous ECG and were classified as known LBBB, as in all previous studies, the exact onset of LBBB was unknown in many patients and LBBB had to be classified as new or presumably new in APACE. This inherent limitation can only be overcome in patients with implantable devices such as pacemakers and loop recorders. In cohort #2 and #3, limited data on previous ECGs were available, therefore differentiation between known LBBB and presumably new LBBB was not possible for all patients. Second, although all three studies tried to be broad in the exact definition of its inclusion criteria in order to reflect the clinical challenge, we wish to acknowledge that it is unclear whether the findings of this study can also be extrapolated to AMI patients presenting with uncommon symptoms such as e.g. exclusively with weakness.(31) Third, our findings were derived from patients presenting with symptoms suggestive of AMI to the ED. While our study designs ensure the generalizability to this setting, our findings may not apply to settings with a much lower pretest probability for AMI such as patients presenting to a

general practitioner, and settings with a much higher pretest probability such as patients in shock or after cardiac arrest transferred directly to a catheter laboratory. Additional studies are necessary in these settings. Fourth, this study required written informed consent. Accordingly, our findings may not apply to critically ill patients unable to provide informed consent, such as patients after cardiac arrest or patients in cardiogenic shock. These patients were eligible only in cohort #2, where a retrospective consent or a consent given by family members was possible. Unfortunately, this limitation also applies to diagnostic tests in general. Fifth, we cannot comment on LBBB in patients with terminal kidney failure, as these patients were excluded in cohort #1 and #3.

In conclusion, most patients presenting with symptoms suggestive of AMI and LBBB to the ED will be found to have diagnoses other than AMI and should not be considered a STEMI equivalent. An integrated triage-algorithm including specific ECG criteria with high specificity, as well as hs-cTnT/I concentrations at presentation and their 0/1h- or 0/2h-changes provides high diagnostic accuracy and efficacy helping in the selection of patients for immediate and/or early coronary angiography.

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Figure Legends

Figure 1 **Integrated diagnostic work-up in cohort #1**

Flowchart representing the integrated diagnostic work-up for patients presenting with left bundle branch block and suspected acute myocardial infarction in cohort #1 using hs-cTnT.

AMI: acute myocardial infarction; LBBB: left bundle branch block; (h)s-cTn: (high) sensitivity-cardiac troponin; pts: patients

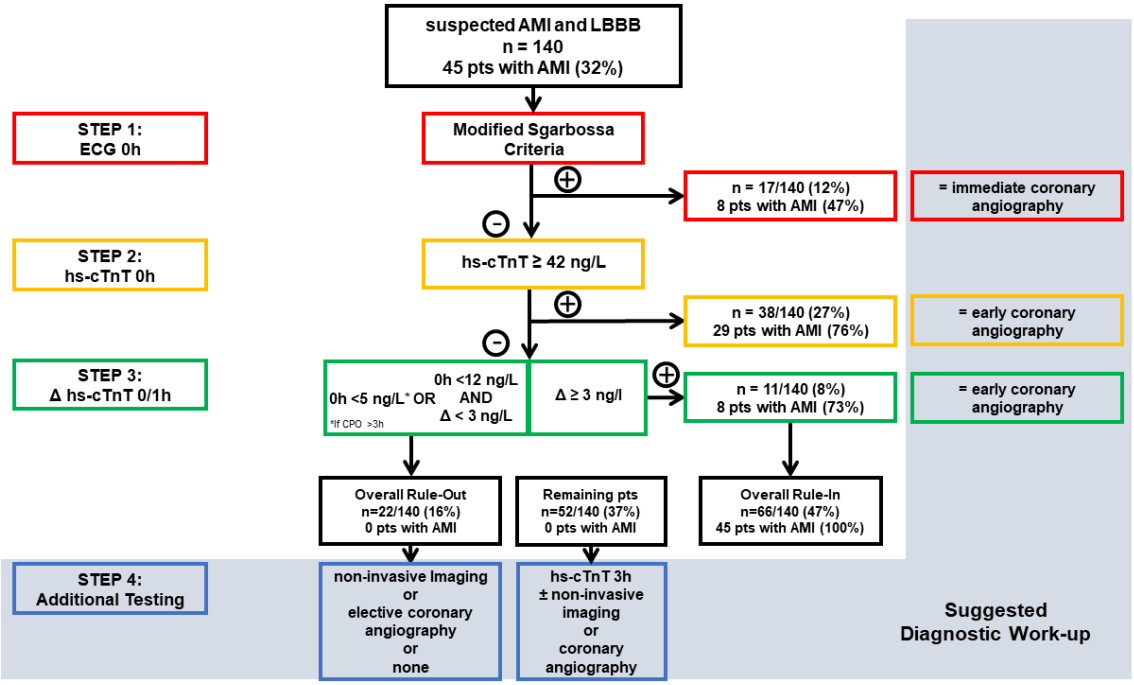

Figure 2 **Integrated diagnostic work-up in cohort #2**

Flowchart representing the integrated diagnostic work-up for patients presenting with left bundle branch block and suspected acute myocardial infarction in cohort #2 using hs-cTnI. 1

patient with LBBB and AMI had not all hs-cTnI measurements at presentation and after 2h available.

AMI: acute myocardial infarction; LBBB: left bundle branch block; (h)s-cTn: (high) sensitivity-cardiac troponin; pts: patients

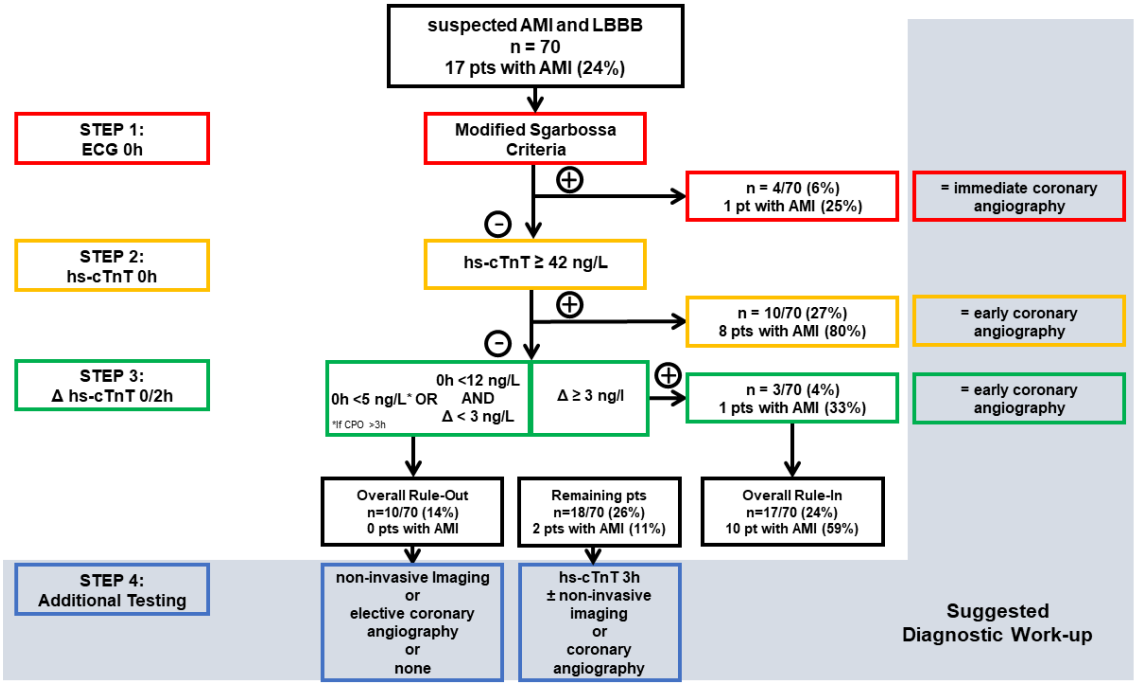

Figure 3 **Integrated diagnostic work-up in cohort #3**

Flowchart representing the integrated diagnostic work-up for patients presenting with left bundle branch block and suspected acute myocardial infarction in cohort #3 using hs-cTnT.

AMI: acute myocardial infarction; LBBB: left bundle branch block; (h)s-cTn: (high) sensitivity-cardiac troponin; pts: patients

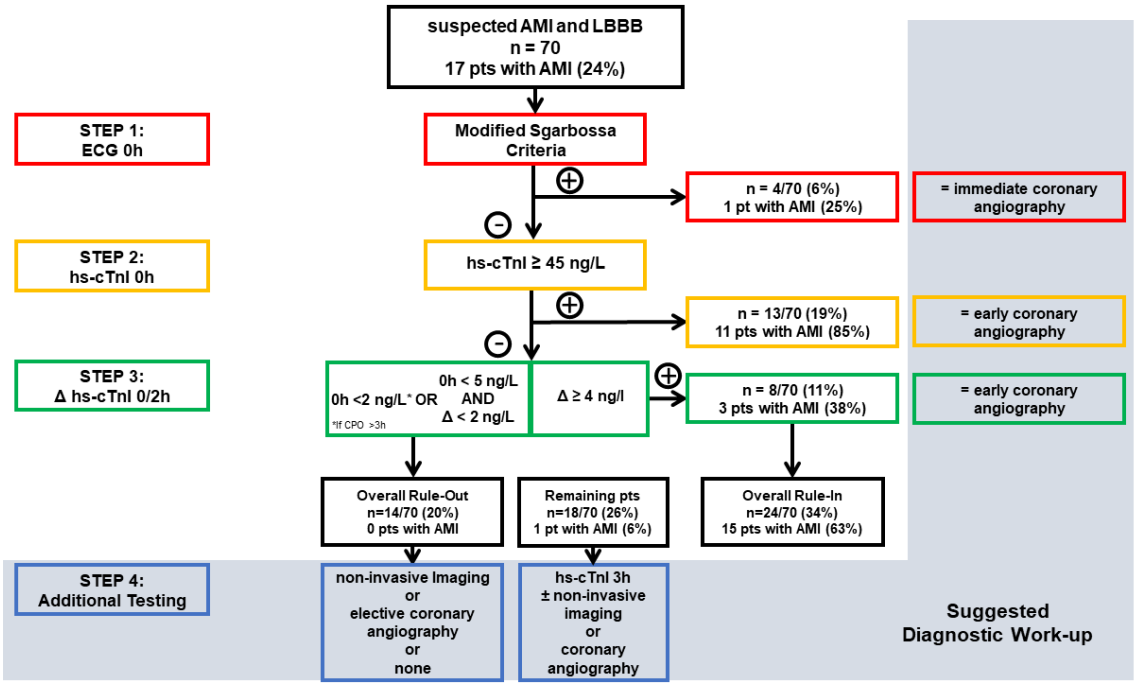
suspected AMI and LBBB
n = 70
17 pts with AMI (24%)
STEP 1:
ECG 0h
Modified Sgarbossa
Criteria
n = 4/70 (6%)
1 pt with AMI (25%)
= immediate coronary
angiography
STEP 2:
hs-cTnI 0h
hs-cTnI ≥ 45 ng/L
n = 13/70 (19%)
11 pts with AMI (85%)
= early coronary
angiography
STEP 3:
Δ hs-cTnI 0/2h
0h < 5 ng/L
0h <2 ng/L* OR AND
Δ < 2 ng/L
*If CPO >3h
Δ ≥ 4 ng/l
n = 8/70 (11%)
3 pts with AMI (38%)
= early coronary
angiography
Overall Rule-Out
n=14/70 (20%)
0 pts with AMI
Remaining pts
n=18/70 (26%)
1 pt with AMI (6%)
Overall Rule-In
n=24/70 (34%)
15 pts with AMI (63%)
STEP 4:
Additional Testing
non-invasive Imaging
or
elective coronary
angiography
or
none
hs-cTnI 3h
± non-invasive
imaging
or
coronary
angiography
Suggested
Diagnostic Work-up

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Table 1 Baseline characteristics in Cohort #1

	all LBBB (n= 140, 100%)		LBBB no AMI (n=95, 68%)		LBBB and AMI (n=45, 32%)		p-value no AMI/AMI
Age, years, median (IQR)	78	(67 - 84)	74	(63 - 81)	82	(76 - 86)	<0.001
Male, sex, n %	93	66%	67	71%	26	58%	0.136
BMI, median (IQR)	27	(24 - 31)	27	(24 - 31)	25	(22 - 30)	0.60
Risk factors, n %							
Hypertension	122	87%	80	84%	42	93%	0.132
Hypercholesterolemia	92	66%	58	61%	34	76%	0.091
Diabetes	25	18%	14	15%	11	25%	0.143
Current smoking	16	11%	10	11%	6	13%	0.63
History of smoking	67	48%	42	44%	25	56%	0.209
History, n %							
Coronary artery disease	76	54%	41	43%	35	78%	<0.001
Previous myocardial infarction	54	39%	26	27%	28	62%	<0.001
Previous revascularization	54	39%	33	35%	21	47%	0.176
Peripheral artery disease	12	8.6%	4	4·2%	8	18%	0.007
Previous stroke	16	11%	7	7·4%	9	20%	0.028
Positive family history	21	17%	17	20%	4	11%	0.27
Medication at entry, n %							
Aspirin/Thienopyridin	77	55%	49	52%	28	62%	0.24
Betablockers	74	53%	47	50%	27	60%	0.24
ACE/AT2- Inhibitors	92	66%	57	60%	35	78%	0.038
Ca- Antagonists	31	22%	16	17%	15	33%	0.028
Marcoumar/Warfarin	27	19%	17	18%	10	22%	0.54
Nitrates	37	26%	21	22%	16	36%	0.092
Measurements/Findings							
Systolic BP, median (IQR)	136	(118 - 161)	138	(121 - 163)	134	(115 - 152)	0.110
Pulse, median (IQR)	82	(67 - 96)	78	(64 - 90)	88	(75 - 99)	0.011
eGFR, mL/min/m2, median	69	(48 - 86)	77	(60 - 91)	47	(35 - 69)	<0.001

(IQR)							
BNP pg/ml, median (IQR)	672	(199 - 1272)	421	(168 - 1121)	919	(327 - 1643)	0.105
Coronary Angiography n (%)	49	35%	24	25%	25	56%	<0.001
One vessel disease	4	2.9%	3	3.2%	1	2.2%	1.000
Two vessel disease	12	8.6%	2	2.1%	10	22%	<0.001
Three vessel disease	21	15%	7	7.4%	14	31%	0.001
Coronary Intervention n (%)	20	14%	4	4.2%	16	36%	<0.001
Left main vessel	0	0.0%	0	0.0%	0	0.0%	n.a.
RIVA	7	5.0%	0	0.0%	7	16%	<0.001
RCX	8	5.7%	2	2.1%	6	13%	0.014
ACD	3	2.1%	1	1.1%	2	4.4%	0.24
Bypass Intervention	6	4.3%	2	2.1%	4	8.9%	0.084
More than one intervention	3	1.1%	1	1.1%	2	4.4%	0.24
CABG	3	2.1%	0	0.0%	3	6.7%	0.032

Table Legends: LBBB: left bundle branch block; IQR: interquartile range; ACE: angiotensin converting enzyme; AT1: angiotension 1; Ca: Calcium; ACS: acute coronary syndrome; BP: blood pressure; eGFR: estimated glomerular filtration rate; RIVA: Ramus interventricularis anterior;
RCX: Ramus circumflexus; ACD: Arteria coronaria dextra; CABG: coronary artery bypass graft

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Table 2 Diagnostic performance of ECG criteria in all cohorts

all cohorts	true-positive test result	false-negative test result	true-negative test result	false-positive test result	Accuracy % (95% CI)	Sensitivity % (95% CI)	Specificity % (95% CI)	NPV % (95% CI)	PPV % (95% CI)
ECG criteria 1 (5 points)	1	74	172	0	70% (64 - 76%)	1% (0 - 7%)	100% (98 - 100%)	70% (64 - 75%)	100% (21 - 100%)
ECG criteria 2 (3 points)	2	73	171	1	70% (64 - 76%)	3% (1 - 9%)	99% (97 - 100%)	70% (64 - 76%)	67% (21 - 94%)
ECG criteria 3 (2 points)	5	70	164	8	68% (62 - 74%)	7% (2 - 15%)	95% (91 - 98%)	70% (64 - 76%)	39% (18 - 65%)
ECG Score ≥ 3 points	2	73	171	1	70% (64 - 76%)	3% (0 - 9%)	99% (97 - 100%)	70% (69 - 71%)	67% (16 - 96%)
Alternative ECG criteria 1 (2 points)	8	67	169	3	72% (66 - 77%)	11% (5 - 20%)	98% (95 - 100%)	72% (66 - 77%)	72% (42 - 91%)
Alternative ECG Score ≥ 3 points	9	66	166	6	71% (65 - 76%)	12% (6- 22%)	97% (93 - 99%)	72% (70 - 73%)	60% (36 - 80%)

Table legends: AUC: area under the curve; CI: confidence interval; NPV: negative predictive value; PPV: positive predictive value, n.a.: not applicable

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Table 3 Diagnostic performance hs-cTn (T and I) and s-cTnI in LBBB patients in all 3 cohorts

cohort #1	AUC	(95% CI)	Cutoff values for PPV 80%	patients, n	true-positive test result, n	false-negative test result, n	true-negative test result, n	false-positive test result, n	Sensitivity % (95% CI)	Specificity % (95% CI)	NPV % (95% CI)	PPV % (95% CI)
hs-cTnT 0h	0.91	(0.85 - 0.96)	≥42ng/L	140	36	9	86	9	80% (66 - 89%)	91% (83 - 95%)	91% (83 - 95%)	80% (66 - 89%)
hs-cTnT Abs Change 0h/1h	0.91	(0.84 - 0.98)	≥3ng/L	120	32	6	75	7	84% (70 - 93%)	92% (83 - 96%)	93% (85 - 97%)	82% (67 - 91%)
hs-cTnI 0h	0.89	(0.83 - 0.95)	≥45ng/L	132	29	13	83	7	69% (54 - 81%)	92% (85 - 96%)	87% (78 - 92%)	81% (65 - 90%)
hs-cTnI Abs Change 0h/1h	0.96	(0.91 - 1.00)	≥4ng/L	111	30	3	71	7	91% (76 - 97%)	91% (83 - 96%)	96% (89 - 99%)	81% (66 - 91%)
s-cTnI 0h	0.97	(0.94 - 1.00)	≥53ng/L	87	28	4	49	6	87% (72 - 95%)	89% (78 - 95%)	93% (82 - 97%)	82% (66 - 92%)
s-cTnI Abs Change 0h/1h	0.93	(0.85-1.00)	≥10ng/L	75	21	4	45	5	84% (65 - 94%)	90% (79 - 96%)	92% (81 - 97%)	81% (62 - 92%)
cohort #2												
hs-cTnT 0h	0.96	(0.85-0.99)	≥42ng/L	45	9	3	31	2	75% (43-95%)	94% (80-99%)	91% (76-98%)	82% (48-98%)
hs-cTnT Abs Change 0h/2h	0.89	(0.74-0.96)	≥3ng/L	42	9	3	24	6	75% (43-95%)	80% (61-92%)	89% (71-98%)	60% (32-84%)
hs-cTnI 0h	0.93	(0.83-0.98)	≥45ng/L	56	13	3	36	4	81% (56-94%)	90% (80-93%)	92% (79-98%)	78% (54-89%)
hs-cTnI Abs Change 0h/2h	0.95	(0.85-0.99)	≥4ng/L	56	15	1	33	7	94% (70-100%)	83% (67-93%)	97% (85-100%)	68% (45-86%)
cohort #3												
hs-cTnT 0h	0.81	(0.67 - 0.95)	≥42ng/L	37	6	7	23	1	46% (23 - 71%)	96% (80 - 99%)	77% (59 - 88%)	86% (49 - 97%)
hs-cTnT Abs Change 0h/1h	0.88	(0.77 - 0.99)	≥3ng/L	37	10	3	17	7	77% (50 - 92%)	71% (51 - 85%)	85% (64 - 95%)	59% (36 - 78%)

s-cTnI 0h	0.96	(0.91 - 1.00)	≥53ng/L	36	1	11	24	0	8% (1 - 35%)	100% (86 - 100%)	69% (52 - 81%)	100% (21 - 100%)
s-cTnI Abs Change 0h/1h	0.92	(0.81 - 1.00)	≥11ng/L	36	9	3	23	1	75% (47 - 91%)	96% (80 - 99%)	88% (71 - 96%)	90% (60 - 98%)

Table legends: LBBB: left bundle branch block; hs-cTn: high sensitivity cardiac troponin: AUC: area under the curve; CI: confidence interval; NPV: negative predictive value; PPV: positive predictive value

n: number of patients

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